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INJECTABLE BIODEGRADABLE BLOCK COPOLYMER GELS FOR USE IN DRUG DELIVERY

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A system and method for the parenteral delivery of a drug in a biodegradable polymeric matrix to a warm blooded animal as an aqueous liquid with the resultant formation of a hydrogel depot for the controlled release of the drug. The system comprises an injectable biodegradable block copolymeric drug delivery liquid having thermal gelation properties. The copolymer has a gel/sol transition temperature such that, above the body temperature of the animal to which it is administered, it is a solution and when administered and cooled to body temperature it forms a hydrogel. The copolymer is made up of (i) a hydrophobic A polymer block of poly (alpha -hydroxy acid) and (ii) a hydrophilic B polymer block comprising a poly(ethylene oxide). The drug is released at a controlled rate from the copolymer which biodegrades into non-toxic products.
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INJECTABLE BIODEGRADABLE BLOCK COPOLYMER GELS FOR USE IN DRUG DELIVERY

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS:

Your petitioners, Byeongmoon Jeong, a citizen of the United States and resident of Utah, whose post office address is 714 S. Arapeen Drive, SLC, UT 84108; You Han Bae, a citizen of the republic of Korea, whose post office address is 103-103, Hundai Apt., Yongbong-dong, Kwanziu 506-303, Korea; Doo Sung Lee, a citizen of the republic of Korea, whose post office address is #300 Yung-Chung Dong Chang An-Ku, Suwon City, Korea 440-746; and Sung Wan Kim a citizen of the United States and a resident of Utah, whose post office address is 1711 Devonshire Drive, SLC, UT 84100, pray that letters patent be granted to them as inventors of INJECTABLE BIODEGRADABLE BLOCK COPOLYMER GELS FOR USE IN DRUG DELIVERY as set forth in the following specification.

The present invention relates to the preparation of thermosensitive biodegradable block copolymers and their use for parenteral or subcutaneous administration of bioactive molecules such as peptide and protein drugs. More particularly, this invention relates to thermosensitive biodegradable polymers containing bioactive molecules having a gel/sol transition temperature that is dependent upon the block length and concentration of the block copolymers. This invention is made possible by the use of thermosensitive biodegradable polymers based on poly(ether-ester) block copolymers, which are described in detail hereinafter. The system is based the discovery that poly(ether-ester) block copolymers having certain molecular weight and composition ranges exist as aqueous solutions at elevated temperatures, e.g. above the gel/sol transition temperature but, when the temperature is lowered below the transition temperature, e.g. to about body temperature, interact to form a semi-solid gel.

BACKGROUND OF THE INVENTION AND SUMMARY OF PRIOR ART

There has been a great deal of research focusing on physicochemical response of stimuli sensitive polymers to changes in temperature, pH, electric field, and chemical substances. Langer, *Science*, **249**, 1527-1533 (1990); Ishihara, et al., *J. Appl. Polym. Sci.*, **29**, 211-217, (1995); Thomas, et al., *J. Am. Chem Soc.*, **117**, 2949-2959, (1995) and Kwon et al., *Nature*, **354**, 291-293 (1991).

Thermosensitive polymers have widely been investigated as drug carriers. Homopolymers or copolymers of N-isopropylacrylamide (NIPAAm) as disclosed by Bae et al., *Makromol. Chem. Rapid Commun.*, **8**, 481-485 (1987) and Chen, et al., *Nature*, **373**, 49-52 (1995) are one type. Another type is triblock copolymers consisting of hydrophobic poly(propylene oxide) as the center block and hydrophilic poly(ethylene oxide) as the side blocks, e.g. Poloxamer brand, as disclosed by Malston, et al., *Macromolecules*, **25**, 5440-5445 (1992). These polymers are generally nonbiodegradable and their toxicities are of concern. For example, following intraperitoneal injections, Poloxamer type copolymers have been shown to enhance plasma cholesterol and triglycerol in rats. Wout et al., *J. Parenteral Sc. & Tech.*, **46**(6), 192-200 (1992).

Much work on polymeric drug delivery systems has focused on injectable microspheres or biodegradable implant systems that require organic solvents during fabrication. Youxin, et al., *J. Controlled Release*, **27**, 247-257 (1993). Because the implant systems possess distinct solid form, they require surgical insertion. Churchill et al., U.S. Patents 4,526,938 and 4,745,160. Surgical implants can result in tissue irritation and damage.

A.S. Sawhney and J.A. Hubbell, *J. Biomed. Mat. Res.*, **24**, 1197-1411 (1990), synthesized terpolymers of d,l-lactide, glycolide and ϵ-caprolactone which degrade rapidly *in vitro*. The hydrophilicity of the material was increased by copolymerization with a polyether surfactant prepolymer (Pluronic F-68). This prepolymer is a block copolymer comprising about 80% w. of a hydrophobic poly(propylene oxide) block and 20% w. of a hydrophilic poly(ethylene oxide) block. It is known that Pluronic type of polymeric surfactants, particularly the poly(propylene oxide) block portions, are not biodegradable.

Other implantable delivery systems, such as shown in Dunn et al, U.S. Patents 4,938,763 and 5,278,202, have also been known for some time. These polymers are either thermoplastic or thermosetting. The thermoplastic solution requires the use of an organic solvent such as N-methyl-2-pyrrolidone, methyl ethyl ketone, dimethylformamide, propylene glycol, THF, DMSO, dodecylazacycloheptan-2-one (Azone) and the like. The thermosetting system

comprises the synthesis of crosslinkable polymers which can be formed and cured in-situ through the use of a curing agent. However, the major drawback of the thermoplastic formulations is the use of organic solvents which can be toxic or irritating to the body tissues. The thermosetting system requires that the drug be admixed with the prepolymer solution prior to additions of the catalysts because the curing reaction is quite rapid and injection must take place almost immediately following the addition of the curing agent.

A.S. Sawhney et al., *Macromolecules*, Vol 26, No. 4, 581-589 (1993) synthesized macromers having a poly(ethylene glycol) central block, extended with oligomers of α-hydroxy acids such as oligo(d,l-lactic acid) or oligo(glycolic acid) and terminated with acrylate groups. Using non-toxic photoinitiators, the macromers can be rapidly polymerized with visible light. Due to the multifunctionality of the macromers, polymerization results in the formation of crosslinked gels. The gels degrade upon hydrolysis of the oligo(α-hydroxy acid) regions into poly(ethylene glycol), the α-hydroxy acid, and oligo(acrylic acid) and their degradation rates can be tailored by appropriate choice of the oligo(α-hydroxy acid) from less than 1 day to up to 4 months. However, in this system, a photoinitiator, an additional component, is employed as well as an additional process such as photocrosslinking. This concept is further exemplified in U.S. Patent 5,567,435.

Cha et al., PCT Publication WO 97/15287 published 1 May 1997, discloses certain block copolymers made up of (i) a hydrophobic A polymer block comprising a member selected from the group consisting of poly(α-hydroxy acids) and poly(ethylene carbonates) and (ii) a hydrophilic B polymer block comprising a polyethylene glycol. These copolymers possess thermal reverse gelation properties in that they form aqueous solutions below the body temperature of the animal to which they are to be administered and gel when the temperature is raised to body temperature.

An optimum material for use as an injectable or implantable polymeric drug delivery device should be biodegradable, be compatible with hydrophilic or

hydrophobic drugs, and allow fabrication with simple, safe solvents, such as water, and not require additional polymerization or reaction following administration.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide block copolymer drug delivery systems that are biodegradable, exhibit thermal gelation behavior and possess good drug release characteristics.

It is also an object of this invention to provide methods to fabricate copolymeric biodegradable thermosensitive drug delivery devices wherein the polymeric matrix can be stored at or below room temperature as a dry, solid dosage form prior to being formed as a solution for administration.

A still further object of this invention is to provide a drug delivery system for the parenteral administration of bioactive agents where there is no requirement for any surgical procedure for implantation.

Yet another object of this invention is to provide a method for the parenteral administration of drugs in a biodegradable polymeric matrix resulting in the formation of a gel depot within the body from which the drugs are released at a controlled rate with the corresponding biodegradation of the polymeric matrix.

These and other objects may be accomplished by a hydrogel drug delivery system utilizing a poly(ethylene oxide) B block and biodegradable poly(α-hydroxide) A block copolymer having both thermosensitivity and biodegradabilty properties. The hydrogel contains an appropriate balance of hydrophilicity (B block) and hydrophobicity (A block) enabling the hydrogel to have thermoreversibility. Furthermore, organic solvents are not used to load such polymer systems with bioactive agents. Therefore, the need to remove any organic solvent is eliminated.

DESCRIPTION OF THE INVENTION

As used herein the following terms shall have the assigned meanings:

"Parenteral" shall mean any route of administration other than the alimentary canal and shall specifically include intramuscular, intraperitoneal, intra-abdominal, subcutaneous, and, to the extent feasible, intravenous.

"Solution," "aqueous solution" and the like, when used in reference to a combination of drug and biodegradable block copolymer contained in such solution, shall mean a water based solution having such drug/polymer combination dissolved or uniformly suspended therein at a functional concentration and maintained at a temperature above the gel/sol transition temperature of the block copolymer.

"Drug delivery liquid" or "drug delivery liquid having thermal gelation properties" shall means a "solution" suitable for injection into a warm-blooded animal which forms a depot upon having the temperature lowered to the body temperature of the subject into which it is administered.

"Depot" means a drug delivery liquid following injection into a warm-blooded animal which has formed a gel upon the temperature being lowered to body temperature.

"Gel," when used, shall mean a semi-solid hydrogel combination of biodegradable block copolymer and water at a temperature below the gel/sol transition temperature which is preferably at or below body temperature.

"Gel/sol transition temperature," "gel/sol transition" or "gelation temperature" or any other similar term shall mean the temperature at which an aqueous combination of the block copolymer undergoes a phase transition between a gel and a solution. Above the gel/sol transition temperature the aqueous combination is a solution and below the gel/sol transition temperature the aqueous combination is a semi-solid hydrogel. The drug will be homogeneously contained in the solution or gel. While it is possible to formulate the block copolymers to have a wide range of gel/sol transition temperatures, it is desirable to have a gel/sol transition temperature that is just above the body temperature of the subject to which an aqueous solution of the block copolymer and drug is to be administered. Since normal body temperature in human beings is about 37°C, a functional range of gel/sol transition temperatures is considered to be between about 30 to 60°C.

"Biodegradable" meaning that the block polymer can break down or degrade within the body to non-toxic components after all drug has been released.

"Drug" shall mean any organic compound or substance having bioactivity and adapted or used for a therapeutic purpose.

"Poly(∝-hydroxy acid)" shall mean a poly(∝-hydroxy acid) polymer *per se* or a poly(∝-hydroxy acid) polymer or copolymer derived from the ring opening polymerization of an ∝-hydroxy acid precursor, such as a corresponding lactide, glycolide or lactone.

"Poly(ethylene oxide)" or "PEO" and "poly(ethylene glycol)" or "PEG" or "polyoxyethylene" may be used interchangeably and shall mean a polymer of ethylene glycol or hydrated ethylene oxide.

Basic to the present invention is the utilization of a block copolymer having hydrophobic or "A" block segments and hydrophilic or "B" block segments. Generally the block copolymer will be a triblock BAB type block copolymer. However, the block copolymer could also be a diblock BA type copolymer.

The biodegradable hydrophobic, or A block, segment is preferably a poly(α-hydroxy acid) member derived or selected from the group consisting of poly(d,l-lactide), poly(l-lactide), poly(d,l-lactide-co-glycolide), poly(l-lactide-co-glycolide), poly(ϵ-caprolactone), poly(γ-butyrolactone), poly(δ-valerolactone), poly(ϵ-caprolactone-co-lactic acid), poly(ϵ-caprolactone-co-glycolic acid-co-lactic acid), hydroxybutyric acid, malic acid and bi- or terpolymers thereof. The above listing is not intended to be all inclusive or necessarily self limiting as combinations or mixtures of the various α-hydroxy acids that can be used to form homopolymeric or copolymeric hydrophobic block segments and still be within the scope of the invention. Generally, any water insoluble biodegradable copolymers can be utilized as the hydrophobic A block including semicrystalline polymers and amorphous polymers. The average molecular weight of such α-hydroxy acid polymeric blocks is between about 500 and 20,000. When formed into diblock copolymers the average molecular weight of the A block is between about 500 and 15,000 and is more preferably between about 700 and 10,000. When formed into triblock copolymers the average molecular weight of the A block is between about 500 and 20,000 and is more preferably between about 700 and 15,000.

The hydrophilic B block segment is poly(ethylene oxide) (PEO) which is also referred to as (polyoxyethylene) or poly(ethylene glycol) (PEG) having an average molecular weight of between about 500 to 25,000 and is more preferably between about 1,000 and 10,000. The same average molecular weight range is applicable to both diblock and triblock type copolymers.

SYNTHESIS

The copolymers of this invention are amphiphilic diblock or triblock copolymers of the structure BA or BAB where B is a hydrophilic block and A is a hydrophobic bidodgradable block.

The diblock copolymers are synthesized by various methods.

Ring Opening Polymerization:

The diblock copolymers may be synthesized by the ring opening polymerization of a cyclic monomer for the biodegradable hydrophobic A block, e.g. L-lactide from one end of a PEO block with or without the use of a catalyst.

The PEO is preferably a mono functional PEO of the formula:

$$X\text{-}(CH_2CH_2O)\text{-}Y\text{-}Z$$

where X is a lower alkoxy group such as methoxy, ethoxy, etc.; Y is a lower alkylene group such as methylene, ethylene, propylene, etc.; and Z is a functional group selected from the group consisting of hydroxyl (OH), amino (NH_2), carboxyl (COOH), thiol (SH) and the like.

Typical are α-methoxy ω-hydroxy PEO ($X=CH_3O, Y=CH_2CH_2, Z=OH$) and α-methoxy ω-amino PEO ($X=CH_3O, Y=CH_2CH_2, Z=NH_2$).

As mentioned above the cyclic monomer can be D,L-lactide, L-lactide), glycolide, D,L-lactide-co-glycolide), L-lactide-co-glycolide, ϵ-caprolactone, γ-butyrolactone, δ-valerolactone, ϵ-caprolactone-co-lactic acid, ϵ-caprolactone-co-glycolic acid-co-lactic acid and the like.

When catalyzed, typical catalysts include stannous octoate, antimony oxide, tin chloride, aluminum isopropoxide, yttrium isopropoxide, sodium, potassium, potassium t-butoxide, sodium t-butoxide and the like.

Typically stannous octoate will be used as the catalyst.

Condensation Polymerization:

The diblock copolymers can also be synthesized by condensation polymerization of an α-hydroxy acid monomer at one end of a PEO block. A monomer such as L-lactic acid, D,L-lactic acid, glycolic acid and the like is used. A PEO such as α-methoxy ω-hydroxy PEO ($X=CH_3O, Y=CH_2CH_2, Z=OH$) or α-methoxy ω-carboxy PEO ($X=CH_3O, Y=CH_2CH_2, Z=COOH$) is used as the PEO source.

Coupling of PEO and poly(α-hydroxy acid) blocks:

Direct coupling of monofunctional PEO with monofunctional biodegradable hydrophobic blocks in the presence of coupling agents is another method in which the coupling agent may be present as a linkage in the copolymer. Coupling agents such as a diisocyanate, e.g. hexamethylene diisocyanate (HMDI); 2,6-toluene diisocyanate; 1,6-toluene diisocyanate; 2,4-toluene diisocyanate; diphenyl methane-4,4' diisocyanate; 3,3'-dimethyl diphenyl methane 4,4'-diisocyanate; (ortho, meta, para)phenylene diisocyanate and the like.

Also, coupling after activation of the functional group with activating agents such as carbonyl diimidazole, succinic anhydride, N-hydroxy succinimide, and p-nitrophenyl chloroformate may be utilized.

The triblock copolymers may be prepared by various means.

Coupling of α-hydroxy acid A block with PEO blocks:

A difunctional biodegradable hydrophobic A block may be coupled with monofunctional PEO to form a BAB copolymer utilizing the coupling techniques mentioned above for the coupling of B and A blocks to form a diblock, e.g. by the use of diisocyanate (DIICN) coupling agents.

In the alternative, diblock copolymers can be coupled using the end functional group of biodegradable hydrophobic B (i.e. poly(α-hydroxy acid), blocks according to the following schematic:

$$BA + AB + DIICN = BA\text{-}DIICN\text{-}AB$$

Ring Opening Polymerization:

Triblock copolymers can also be prepared by ring opening polymerization of ethylene oxide at both ends of a biodegradable hydrophobic A block, e.g.

poly(α-hydroxy acid), or by sequential ring opening polymerization of cyclic monomers for the biodegradable hydrophobic block, e.g. L-lactide, followed by ethylene oxide (another cyclic monomer for PEO).

Both diblock BA and triblock BAB type hydrophilic/hydrophobic block copolymers synthesized as disclosed herein possess thermal gelation properties and are biodegradable. BAB type block copolymers possess some similarities to the Poloxamer or Pluronic systems described above, but are quite different in that the hydrophobic poly(α-hydroxy acid) A block is biodegradable and more biocompatible than the hydrophobic PPO block of the Poloxamer Pluronic system.

As noted, the B block is formed from appropriate molecular weights of hydrophilic poly(ethylene oxide) (PEO). PEO was chosen as the hydrophilic water-soluble block domain because of its unique biocompatibility, nontoxicity, micelle forming properties, and rapid clearance from the body.

The hydrophobic A blocks are synthesized and utilized because of their biodegradable and biocompatible properties. The *in vitro* and *in vivo* degradation of these hydrophobic polymer blocks is well understood and the degradation products are natural metabolites that are readily eliminated by the body.

The molecular weight of the hydrophobic poly(α-hydroxy acid) A blocks, relative to that of the water-soluble B PEG block, is regulated to retain desirable water-solubility and gelling properties. Also, the proportionate weight ratios of hydrophilic B block to the hydrophobic A block must also be sufficient to enable the block copolymer to possess good water solubility at the required concentrations at temperatures above body temperature. Generally, biodegradable block copolymers possessing desired thermal gelation properties are prepared wherein the hydrophilic B block makes up about 20 to 90% by weight of the copolymer and the hydrophobic A blocks makes up about 10 to 80% by weight of the copolymer. Preferably the hydrophilic B block will make up between about 25 to 75% by weight of the copolymer, and the hydrophobic biodegradable A block will also make up between about 25 to 75% by weight.

All resulting diblock and triblock copolymers should be soluble in aqueous solutions at functional concentrations. There is a minimum concentration for each

copolymer for gelation, i.e. the gel/sol transition temperature, by lowering the temperature. Also, if concentrations are too high, aqueous solutions will be too viscous to inject parenterally. The only concentration parameter that is critical is that under which the polymer is functional.

Therefore, the concentration at which the block copolymers are soluble at temperatures to be utilized for parenteral administration may be considered as the functional concentration. Generally speaking, block copolymer concentrations in the range of about 5 to 60% are in the functional range and concentrations in the range of between about 10 to 50% by weight are preferred. In order to obtain a viable phase transition of the polymer, a certain minimum concentration is required.

The mixture of the biodegradable polymer and bioactive agents or drugs may be prepared as an aqueous solution at a higher temperature than the gelation temperature of the polymeric material. Once injected into the body via intramuscular, subcutaneous or intraperitoneal route as a liquid, the drug/polymer formulation will undergo a phase change and will preferably form a highly swollen gel, since body temperature will be below the gelation temperature of the material.

This system will cause minimal toxicity and mechanical irritation to the surrounding tissue due to the biocompatibility of the materials and will be completely biodegradable within a specific predetermined time interval. Once gelled, the drug release from the polymeric matrix can be controlled by proper formulation of the various copolymer blocks.

The only limitation as to how much drug can be loaded onto the copolymer is one of functionality. Generally speaking, the drug can make up between about 1 to 60 % by weight of the drug polymer combination with ranges of between about 5 to 30 % being preferred.

This invention is applicable to the delivery of any drug that is stable in the solution as prepared and that will release from the hydrogel matrix following administration. It would serve no useful purpose to attempt to catalog drugs as it will be readily apparent to those skilled in the art the type of drugs that can be used

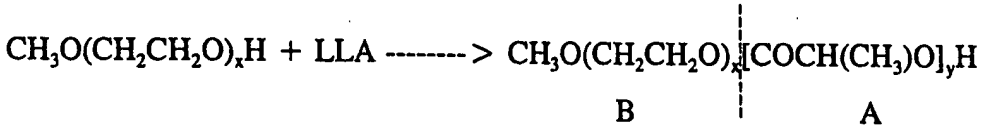
and minimal experimentation will be required to prove the viability of the invention as to any particular drug or class of drugs.

The invention may be particularly useful in the delivery of peptide or protein based drugs. However, in general, the invention may be useful in the delivery of a broad category of bioactive agents or drugs such as therapeutic agents in all of the major therapeutic areas including, but not limited to, anti-infectives such as antibiotics and antiviral agents, analgesics and analgesic combinations, anorexics, antidiarrheal, antihistamines, anti-inflammatory agents, antimigraine preparations, antimotion sickness agents, antinauseants, antineoplastic, antiparkinsonism drugs, antipruritic, antipsychotic, antipyretics, antispasmodics including gastrointestinal and urinary, anticholinergic, sympathomimetic, xanthine derivatives, cardiovascular preparations including calcium channel blockers, beta-blockers, antiarrythmics, antihypertensives, diuretics, vasodilator including general coronary, peripheral and cerebral, central nervous system stimulants including cough and cold preparations, decongestants, diagnostics, hormones, immunosupressives, muscle relaxants, parasympatholytic, parasympathomimetic, psychostimulants, sedatives and tranquilizers.

Within the guidelines stated herein, one skilled in the art can determine, without undue experimentation, the appropriate drug loading, polymer composition and concentration, degradation rates, degree of gelation/emulsion formation, etc.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

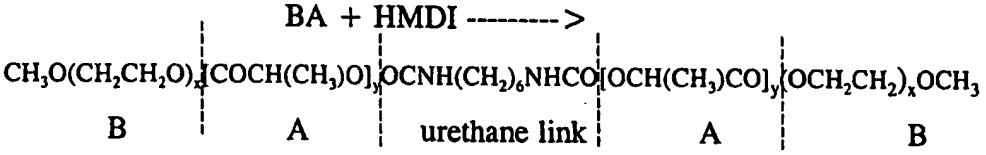
In order to illustrate preferred embodiments of this invention, both diblock BA copolymers and triblock BAB copolymers were synthesized. The diblock BA copolymers consisting of PEO/PLLA were synthesized by ring opening polymerization of L-lactide (LLA) on monomethoxy poly(ethylene oxide) (PEO) according to the reaction scheme shown in Formula I:



Formula I

where x and y are integers suitable for the preparation of copolymers having the block molecular weights as shown above.

The triblock BAB copolymers were synthesized by coupling the diblock BA copolymer of Formula I using hexamethylene diisocyanate (HMDI) as a coupling agent according to the reaction scheme shown in Formula II:



Formula II

In both reaction schemes depicted in Formulas 1 and 2 the hydrophilic B block can be prepared using various molecular weights of poly(L-lactic acid) PLLA) and poly(ethylene oxide) (PEO).

EXAMPLE 1

Synthesis of BA Di-Block Copolymers (PEO-PLLAA-OH)

Following the reaction scheme of Formula I, methoxy poly(ethylene oxide)(PEO)(MW: 5000) (8 g) was dissolved in 80 ml of dried toluene. Residual water was removed by azeotropic distillation to a final volume of 30 ml. Then, polymerization of L-lactide (LLA) (4.4 g) and stannous octoate (8.7 mg) onto PEO was carried out in this solution and refluxed under a dry nitrogen atmosphere for 24 hours. The solution was precipitated in diethyl ether and the residual solvent was eliminated by vacuum after filtering. The conversion was over 90%. Diblock BA copolymers were prepared wherein the A block had molecular weights of 720, 1000, 1730 and 1960.

Other diblock copolymers including poly(ethylene oxide-DL-lactic acid)(PEO-PDLLA; poly(ethylene oxide-(DL-lactic acid-co-glycolic acid)), (PEO-P(DLLA/GA)), and poly(ethylene oxide-(DL-lactic acid-co-ϵ-caprolactone)), (PEO-P(DLLA/CL)) were also synthesized.

EXAMPLE 2

Synthesis of Diblock Copolymers (PEO-P(DLLA/GA)).

Monomethoxy PEO (10 g) was added in 200 ml of dried toluene. Residual water was removed by azeotropic distillation and in this case, all of the toluene was

removed by distillation. DL-lactide (2.5 g) and glycolide (3 g) and stannous octoate (10.87 mg) were added to PEO/toluene and heated at 160°C in an oil bath under dry nitrogen atmosphere for 24 hours. The reaction mixture was dissolved in methylene chloride, precipitated in diethyl ether, and the residual solvent was eliminated by vacuum after filtering. The conversion was over 90%.

EXAMPLE 3

Synthesis of BAB Tri-Block Copolymers (PEO-PLLA-PEO).

A BA Di-block ((PEO-PLLA-OH), MW: 5000-2560) was added to 200 ml of dried toluene. Residual water was removed by azeotropic distillation to a final volume of 70 ml. HMDI (55.59 mg) and stannous octoate (5.356 mg) were added to the solution, stirred at 60°C for 12 hours and then gently refluxed for 6 hours under a dry nitrogen atmosphere. The resulting triblock copolymers were purified by fractional precipitation of the copolymers out of methylene chloride using diethyl ether. The coupling reaction was monitored by GPC. The yield of triblock copolymer after fractional precipitation was 50%. The copolymers were stored in a refrigerator under nitrogen gas. Other triblock copolymers were synthesized by the same method.

The resulting triblock copolymers consisted of two B (PEO) blocks having a molecular weight of 5000 each and a central A (PLLA) block having molecular weights of 2040, 3000 and 5000 respectively.

EXAMPLE 4

Gel/sol transition temperatures of the various BA and BAB copolymers at given concentrations (wt/wt%)

All block copolymers shown in Table 1 were soluble in water at the stated concentrations above the gel/sol transition temperature shown. Initially, the polymers were dissolved in distilled water at an elevated temperature at the stated concentrations and placed in a tightly sealed 4 ml vial. The vials were cooled below the gelation temperature and stored at 4°C for 12 hours. The gel/sol transition temperature was defined by the gel melting temperature. The gels were equilibrated for 20 minutes at a given temperature in a water bath. Gel melting was measured by increasing the temperature 2°C/step. A gel was defined as having no

flow in one minute after rotating 90° in the bath. All gels showed thermosensitivity and the gel/sol phase transition occurred within a narrow temperature range. Transition temperatures and concentrations shown in Table 1 are approximations extrapolated from graphs showing gel/sol transition curves plotting temperature vs. concentration but are sufficient to demonstrate the influence of molecular weight of A and B blocks, relative amount of A vs.B block content and concentration of copolymers on the gel/sol transition temperature.

Table 1

Copolymer Type	MW of Copolymer Blocks (BA or BAB*)	Transition Temp(°C)	Conc. (wt/wt)
BA	5000:720	25	30
BA	5000:720	35	35
BA	5000:720	47	40
BA	5000:720	55	45
BA	5000:720	57	50
BA	5000:720	65	60
BA	5000:1000	45	35
BA	5000:1000	55	40
BA	5000:1000	60	45
BA	5000:1000	65	50
BA	5000:1730	20	20
BA	5000:1730	45	25
BA	5000:1730	75	30
BA	5000:1730	95	35
BA	5000:1960	20	15
BA	5000:1960	45	20
BA	5000:1960	85	25
BA	5000:1960	90	30
BAB	5000:2040:5000	20	18
BAB	5000:2040:5000	30	20
BAB	5000:2040:5000	40	22
BAB	5000:2040:5000	60	25
BAB	5000:2040:5000	75	30
BAB	5000:3000:5000	20	17
BAB	5000:3000:5000	40	20
BAB	5000:3000:5000	55	23
BAB	5000:3000:5000	60	25
BAB	5000:3000:5000	75	30
BAB	5000:5000:5000	0	11
BAB	5000:5000:5000	25	13
BAB	5000:5000:5000	40	16
BAB	5000:5000:5000	65	23

B=PEO A=PLAA

Aqueous solutions of diblock BA (PEO-PLAA) and triblock (PEO-PLLA-PEO) copolymers formed micelles at low concentrations and became gels above a certain concentration. The micelle packing is thought to be the mechanism of gelation for these block copolymers. Contrary to the Poloxamer or Pluronic type of copolymers, the above described copolymers form a gel at lower temperatures

and become a sol at higher temperatures. In other words, they do not exhibit reverse thermal gelation but follow a more traditional route in that they form solutions at higher temperature and solidify or gel as the temperature is lowered. By changing the biodegradable block length, the sol/gel transition temperature can be easily manipulated as shown in Table 1. By decreasing the PLLA block length, the gel/sol transition can be shifted toward higher concentrations. Selected block copolymers, i.e. 25% aqueous solution of PEO-PLLA (5000:1730) or 22% aqueous solution of PEO-PLLA-PEO (5000:2040:5000), form gels at body temperature (37°C) and become a sol above body temperature at a given concentration.

These polymers combined with appropriate amounts of bioactive agents can be dissolved in water above body temperature (i.e. 45°C). Due to the temperature dependent phase transition, the sol becomes a gel after subcutaneous injection into the body. As a gel within the body, it acts as a sustained release matrix.

Based on the thermosensitivity and biodegradability of these block copolymers, a solvent-free (i.e. no organic solvent) injectable system can be designed as a controlled drug carrier. This system has numerous advantages over common drug delivery systems. First, the formulation is simple and requires no organic solvent. In addition, the designed matrix, if desired, can be stored at or below room temperature as a dry, solid dosage form before administration. Also, there is no requirement for a surgical procedure for implantation. The system is biodegradable and possesses the typical advantages of hydrogels, e.g., little or no tissue irritation and improved biocompatability.

The above description will enable one skilled in the art to make and use drug loaded block copolymers based on thermal gelation properties. The description is not intended to be an exhaustive statement of specific drugs which can be utilized and loaded onto the biodegradable block copolymers. Neither are all block copolymers which may be prepared specifically shown. It will be apparent to one skilled in the art that various modifications may be made without departing from the scope of the inventions which is limited only by the following claims and their functional equivalents.

CLAIMS

We claim:

1. An injectable aqueous biodegradable block copolymeric drug delivery system having thermal gelation properties such that said system is a solution above the thermal gelation temperature and a hydrogel at or below said thermal gelation temperature said system comprising an aqueous carrier having contained therein:

(a) an effective amount of a drug intimately contained in

(b) an effective concentration of a biodegradable block copolymer comprising

(i) a hydrophobic A polymer block comprising a poly(α-hydroxy acid) and

(ii) a hydrophilic B polymer block comprising a poly(ethylene oxide).

2. The system according to claim 1 wherein the hydrophobic A polymer block is selected from the group comprising; poly(d,l-lactide), poly(l-lactide), poly(d,l-lactide-co-glycolide), poly(l-lactide-co-glycolide), poly(ϵ-caprolactone), poly(γ-butyrolactone), poly(δ-valerolactone), poly(ϵ-caprolactone-co-lactic acid), poly(ϵ-caprolactone-co-glycolic acid-co-lactic acid), hydroxybutyric acid, malic acid, bipolymers thereof and terpolymers thereof.

3. The system according to claim 2 wherein the effective concentration of the biodegradable block copolymer in said aqueous carrier is between about 5 and 60% by weight.

4. The system according to claim 3 wherein the hydrophobic A block content of the biodegradable block copolymer is between about 10 to 80% by weight and the hydrophilic B block content of the biodegradable block copolymer is between about 20 to 90% by weight.

5. The system according to claim 4 wherein said diblock copolymer has a gel to sol transition temperature between about 30 and 60°C.

6. The system according to Claim 4 wherein said block copolymer is a BA type diblock copolymer.

7. The system according to claim 6 wherein the weight average molecular weight of the A polymer block is between about 500 and 15,000 and the weight average molecular weight of the B polymer block is between about 500 and 25,000.

8. The system according to claim 7 wherein the weight average molecular weight of the A polymer block is between about 700 and 10,000 and the weight average molecular weight of the B polymer block is between about 1,000 and 10,000.

9. The system according to claim 4 wherein said block copolymer is a BAB type triblock copolymer.

10. The system according to claim 3 wherein the weight average molecular weight of the A polymer block is between about 500 and 20,000 and the weight average molecular weight of the B polymer block is between about 500 and 25,000.

11. The system according to claim 10 wherein the weight average molecular weight of the A polymer block is between about 700 and 15,000 and the weight average molecular weight of the B polymer block is between about 1,000 and 10,000.

12. The system according to claims 6 and 9 wherein the effective amount of the drug intimately contained in said block copolymer is between about 1 and 60% by weight of the drug copolymer combination.

13. The system according to claim 12 wherein the effective amount of the drug intimately contained in said block copolymer is between about 5 and 30% by weight of the drug copolymer combination.

14. A biodegradable block copolymer comprising:

(i) a hydrophobic A polymer block comprising a poly(α-hydroxy acid) and

(ii) a hydrophilic B polymer block comprising a poly(ethylene oxide) and where,

the block copolymer contains between about 10 and 80% by weight of the hydrophobic A polymer block and between about 20 and 90% by weight of the hydrophobic B polymer block.

15. The block copolymer according to claim 14 wherein the block copolymer is thermally sensitive in an aqueous carrier undergoing a transition from a gel state at a lower temperature to a sol state at a higher transition temperature.

16. The block copolymer according to claim 15 wherein the hydrophobic A polymer block is selected from the group comprising; poly(d,l-lactide), poly(l-lactide), poly(d,l-lactide-co-glycolide), poly(l-lactide-co-glycolide), poly(ϵ-caprolactone), poly(γ-butyrolactone), poly(δ-valerolactone), poly(ϵ-caprolactone-co-lactic acid), poly(ϵ-caprolactone-co-glycolic acid-co-lactic acid), hydroxybutyric acid, malic acid, bipolymers thereof and terpolymers thereof.

17. The block copolymer according to Claim 16 wherein said block copolymer is a BA type diblock copolymer.

18. The block copolymer according to claim 17 wherein the weight average molecular weight of the A polymer block is between about 500 and 15,000 and the weight average molecular weight of the B polymer block is between about 500 and 25,000.

19. The block copolymer according to claim 18 wherein the weight average molecular weight of the A polymer block is between about 700 and 10,000 and the weight average molecular weight of the B polymer block is between about 1,000 and 10,000.

20. The block copolymer according to claim 16 wherein said block copolymer is a BAB type triblock copolymer.

21. The block copolymer according to claim 20 wherein the weight average molecular weight of the A polymer block is between about 500 and 20,000 and the weight average molecular weight of the B polymer block is between about 500 and 25,000.

22. The block copolymer according to claim 21 wherein the weight average molecular weight of the A polymer block is between about 700 and 15,000

and the weight average molecular weight of the B polymer block is between about 1,000 and 10,000.

23. The block copolymer according to claims 17 and 20 wherein said block copolymer additionally contains an effective amount of a drug intimately contained therein.

24. The block copolymer according to claim 23 wherein the amount of the drug intimately contained in said block copolymer is between about 1 and 60% by weight of the drug copolymer combination.

25. The block copolymer according to claim 24 wherein the effective amount of the drug intimately contained in said block copolymer is between about 5 and 30% by weight of the drug copolymer combination.

26. A method for the parenteral delivery of a drug in a biodegradable polymeric matrix to a warm blooded animal as a liquid with the resultant formation of a gel depot within said animal for the controlled release of said drug, which comprises:

(1) providing an injectable aqueous biodegradable block copolymeric drug delivery system having thermal gelation properties such that said system is a solution above the thermal gelation temperature and a hydrogel at or below said thermal gelation temperature said system comprising an aqueous carrier having contained therein:

(a) an effective amount of a drug intimately contained in

(b) an effective concentration of a biodegradable block copolymer comprising

(i) a hydrophobic A polymer block comprising a poly(α-hydroxy) acid and

(ii) a hydrophilic B polymer block comprising a poly(ethylene oxide).

(2) maintaining said composition as a liquid at a temperature above the gel/sol transition temperature of said block copolymer in said aqueous carrier; and

(3) injecting said liquid parenterally into said warm blooded animal forming a gel depot of said drug and biodegradable block polymer as the temperature of the liquid is lowered by the body temperature of said animal below said gel/sol transition temperature.

27. The method according to claim 26 wherein the hydrophobic A polymer block is selected from the group comprising: poly(d,l-lactide), poly(l-lactide), poly(d,l-lactide-co-glycolide), poly(l-lactide-co-glycolide), poly(ϵ-caprolactone), poly(γ-butyrolactone), poly(δ-valerolactone), poly(ϵ-caprolactone-co-lactic acid), poly(ϵ-caprolactone-co-glycolic acid-co-lactic acid), hydroxybutyric acid, malic acid, bipolymers thereof and terpolymers thereof.

28. The system according to claim 27 wherein the effective concentration of the biodegradable block copolymer in said aqueous carrier is between about 5 and 60% by weight.

29. The method according to claim 28 wherein the hydrophobic A block content of the biodegradable block copolymer is between about 10 to 80% by weight and the hydrophilic B block content of the biodegradable block copolymer is between about 20 to 90% by weight.

30. The method according to Claim 29 wherein said block copolymer is a BA type diblock copolymer.

31. The method according to claim 30 wherein the weight average molecular weight of the A polymer block is between about 500 and 15,000 and the weight average molecular weight of the B polymer block is between about 500 and 25,000.

32. The method according to claim 31 wherein the weight average molecular weight of the A polymer block is between about 700 and 10,000 and the weight average molecular weight of the B polymer block is between about 1,000 and 10,000.

33. The method according to claim 29 wherein said block copolymer is a BAB type triblock copolymer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16418

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/10; C08K 13/02; C08L 67/04, 71/02
US CL :424/422, 486; 523/113; 524/916; 525/450, 533

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/422, 486; 523/113; 524/916; 525/450, 533

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 4,877,606 A (CHURCHILL et al.) 31 October 1989, abstract, column 3, line 64 to column 4, line 10, column 4, line 42 to column 5, line 46, column 6, lines 7-19 and examples 1, 4 and 6.	1-11, 14-22 --------- 1-11, 14-22, 26-35
X -- Y	US 4,492,035 A (CHURCHILL et al.) 17 July 1990, abstract, column 2, line 39 to column 3, line 45, column 4, lines 24-25, column 5, lines 28-49 and examples 1-2 and 10.	1-11, 14-22 ---------- 1-11, 14-22, 26-35
X	US 4,438,253 A (CASEY et al.) 20 March 1984, abstract, column 3, line 24 to column 4, line 33.	14
Y	US 5,306,501 A (VIEGAS et al.) 26 April 1994, abstract, column 2, lines 26-47 and column 5, line 42 to column 7, line 10.	26-35

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 09 DECEMBER 1998	Date of mailing of the international search report 31 DEC 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ANDREW E.C. MERRIAM Telephone No. (703) 308-2351

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16418

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 12-13, 23-25, 36-37
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.